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Indications/Uses

Idiopathic Pulmonary Fibrosis

Fibrosis
Scarring is the body's normal wound healing response in which specialized cells called fibroblasts deposit layers of collagen, a ubiquitous protein that helps form a scar. Sometimes the normal wound healing response goes awry, and the formation of scar **tissue** occurs faster than collagen is naturally broken down. The excessive production and deposition of collagen results in pathological scarring, a process called **fibrosis**.

Fibrosis causes normal **tissue** to be replaced by scar **tissue**; organs become stiff and cannot perform functions essential to life and health. The progression of fibrotic disease can lead to organ failure and death. **Fibrosis** can be triggered by a variety of events including trauma, surgery, infection, environmental pollutants, alcohol, and other types of toxins.

Fibrosis affects all major organs
Fibrosis, much like inflammation, is one of the major, classic pathological processes in medicine. It is a key component of multiple diseases that affect millions of people worldwide including: idiopathic pulmonary **fibrosis** (lung **fibrosis** of unknown origin); scleroderma (thickening of the skin); diabetic retinopathy and age-related macular degeneration (fibrotic diseases of the eye and leading causes of blindness); diabetic nephropathy, glomerulosclerosis and IgA nephropathy (causes of kidney failure and the need for dialysis and retransplant); cirrhosis and biliary atresia (leading causes of liver **fibrosis** and failure) and congestive heart failure.

Unlike inflammation, for which anti-inflammatory therapies abound, there are no approved treatments that directly target the process of **fibrosis** despite its preponderance and potentially fatal consequences in so many diseases. Current therapies for fibroproliferative disorders usually include anti-inflammatory drugs, which are palliative at best and fail to address the fibrotic process that causes disease progression. There is a large unmet need for a safe and effective anti-fibrotic therapy that delays disease progression and reduces mortality.

Idiopathic pulmonary fibrosis (IPF)
IPF is a debilitating and life-threatening lung disease characterized by a progressive scarring of the lungs that hinders oxygen uptake. The cause of IPF is not known. As scarring progresses, patients with IPF experience shortness of breath and difficulty with performing routine functions, such as walking and talking. The prevalence of IPF has been estimated to be over 50,000 cases in the U.S., with an annual incidence of approximately 15,000. There are no FDA-approved treatments for IPF, and approximately two-thirds of patients die within five years after diagnosis. Patients are typically treated with anti-inflammatory agents; however, none have been clinically proven to improve survival or quality of life for patients with IPF.

Connective tissue growth factor (CTGF) mediates fibrosis
A growing body of clinical evidence supports the role of CTGF in fibrotic disease. Numerous published studies show that CTGF is overexpressed (present in abnormally high amounts) in samples obtained from patients with fibroproliferative disorders of the major organs and tissues including the lungs, skin, kidneys, liver, heart, and eyes.

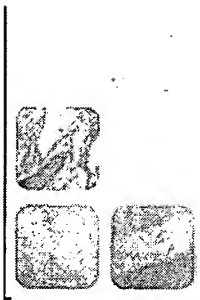
In IPF, CTGF has been implicated in all levels of the disease from increased CTGF gene expression to elevated levels of CTGF protein in the cells thought to play an active role in the disease. Researchers have reported increased expression of the CTGF gene in transbronchial-biopsy specimens and bronchoalveolar lavage cells. Further, the presence of CTGF protein in lung **tissue** of IPF patients appears to be confined predominantly to those cell types believed to play a critical role in pulmonary **fibrosis** (proliferating type II alveolar cells and activated fibroblasts).

Anti-CTGF therapy: new approach to treating fibrosis
Targeting CTGF to inhibit the fibrotic process is supported by independent studies and FibroGen's preclinical work. **Fibrosis** was successfully treated with antibodies targeting CTGF in animal models of systemic sclerosis and kidney and lung fibrotic disease, including a model of bleomycin-induced lung **fibrosis**.

Other studies show that CTGF is a downstream mediator responsible for the persistent pro-fibrotic effects of transforming growth factor-beta (TGF-beta), indicating the importance of targeting CTGF to treat diseases marked by chronic **fibrosis**. TGF-beta is a regulatory protein that has multiple functions, including an early role in the inflammatory response to injury and a central role in triggering the chain of events leading to the induction of CTGF and scarring. Due to its specialized role in perpetuating the scarring process, CTGF could be a more specific target for anti-fibrotic therapies, which could provide significant clinical benefit without broad side effects.

More information related to FibroGen's work on selective inhibition of TGF-beta can be found on the R&D section of this Web site.

Clinical development of FG-3019
FibroGen is developing FG-3019, a recombinant fully human monoclonal antibody to CTGF, for the treatment of fibrotic diseases, complications of diabetes, and pancreatic cancer. FG-3019 is designed to bind and neutralize CTGF. In animal models of lung, kidney, and systemic **fibrosis** including heart and liver, treatment with FG-3019 reduces scar **tissue** formation and preserves organ structure and function. FibroGen has completed the treatment phase of a Phase 1 study of FG-3019 in patients with IPF.



More information on FG-3019 can be found in the Products in Development section of this Web site.

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